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EXAMINER	
EPPS, JANET L	

ART UNIT	PAPER NUMBER
1635	17

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/640,279	SANGHVI ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 20-41* is/are rejected.

7)☒ Claim(s) *16-19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Arguments

1. Applicant's arguments with respect to claims 1-15, and 20-41 have been considered but are moot in view of the new ground(s) of rejection set forth below.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 22-26, and 28-34 are rejected under 35 USC 102(b) as being anticipated by Caruthers et al. (US 5,750,666)

Caruthers et al. disclose a method for synthesizing polynucleotides wherein said method comprises deprotection of a 5'-tritylated nucleoside attached to a solid support via acid catalysis (col. 52, lines 54-55). The deprotected 5'-O of the nucleoside attached to the solid support is then reacted with a 5'-dimethoxytrityl nucleoside-3'-aminophosphine (col. 52, lines 56-57). The next step comprises a capping step wherein the unreacted moieties are capped or blocked with acetic anhydride and N-methylimidizole (col. 52, lines 57-59). Oxidation is then carried out by reaction with aqueous iodine (col. 52, lines 59-61). The modified polynucleotide is then cleaved from the support, and the base and phosphate-protecting groups removed by treating the polymer-supported polynucleotide with concentrated ammonium hydroxide, i.e. wherein the protecting groups are base labile and stable in acid (col. 53, lines 38-40). See example XX

wherein an oligonucleotide of 18 nucleotides in length was synthesized, comprising the heterocyclic base moiety adenine (col. 53, line 36).

Additionally, in another embodiment of Caruthers et al. the nucleoside monomers, used for coupling to the deprotected 5'-O- of the nucleoside or oligonucleoside attached to the support, comprise a 3'-O activated modified phosphorous group (see compound Ia, col. 3), wherein M is a heteroatom such as sulfur, oxygen or nitrogen (col. 4, lines 59-60), and X is a secondary amino group NR6R7, wherein R6 and R7 when taken together form (*inter alia)* an alkylene chain, or taken separately represent substituted or unsubstituted alkyl, aryl or aralkyl groups (col. 5, lines 18-30). In another embodiment X can be derived to include a morpholine group (col. 5, line 60).

Furthermore, in a specific embodiment of Caruthers et al., a method for synthesizing phosphorodithioate linkages was disclosed. This process comprised the use of dialkylaminothionucleoside phosphines in the coupling reaction, and after the coupling step the resulting thiophosphotiodiester was then treated with a sulfurizing agent comprising 5% elemental sulfur in carbon disulfide/pyridine/triethylamine, carbon disulfide in pyridine was then added to remove the excess sulfurizing agent, there was no mention of a separate capping step in this example (col. 53, lines 21-30).

Caruthers et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-8, 12-14, 20-21, 31, 33-34, and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirschbein in view of Agrawal et al.

Hirschbein discloses a method of synthesizing an oligomer comprising deblocking a blocked functionality, usually a 5'-tritylated hydroxyl (steps (a-b) instant claim 1) on the growing correct-sequence chain, or on the initial monomer attached to a solid phase support, to form a reactive functionality, such as a 5'-hydroxyl. Next the reactive functionality is reacted with a blocked and protected nucleoside phosphoramidite or phosphorthioamidite monomer or analog thereof (coupling step (c) of claim 1), usually in the presence of an activator, such as tetrazole (claims 20-21). The unreacted functionalities are capped (step (d) claim 1), and then oxidized. (col. 4, lines 51-68). The oxidation and capping steps can be reversed. (col. 5, lines 1-4). Hirschbein used this process for synthesizing a 22-base phosphorothioate (anticipates claims 39-41), except that in place of the oxidation step, a sulfurization step was substituted, in other words, the synthesis consisted of repeated cycles of detritylation, coupling, sulfurization, and capping (col. 5, lines 41-50, anticipates claim 12 since the sulfurizaton step comprises the transfer of sulfur using a thiuram disulfide). The 22-mer was cleaved from the support and deprotected with concentrated ammonium hydroxide (col 5, lines 62-63; anticipates claims 2-5, 33-34). The sulfurization step comprises, preferably wherein, a thiuram disulfide is delivered to

the growing oligomer in a suitable organic solvent, such as acetonitrile, tetrahydrofuran, dichloromethane, or the like in a concentration of 0.01 M to about 2.0 M (col. 5, lines 15-20).

However, Hirschbein does not explicitly disclose a method for synthesizing an oligomer wherein the oxidizing agent that transfers a sulfur atom is dimethylthiuram disulfide. Moreover, Hirschbein does not teach treating an extended compound with a mixture comprising an oxidizing and capping reagents in a single step.

Hirschbein does not explicitly disclose wherein the sulfur transfer reagent is dimethylthiuram disulfide, however Hirschbein does disclose wherein the thiuram disulfides used in the disclosed method of synthesizing sulfurized oligonucleotides preferably has a structure according to formula I (col. 2, lines 46-68). This compound is encompassed by formula I of Hirschbein, specifically wherein at least two of any one of R1-R4 are hydrogen, and the remaining groups of R1-R4 are methyl groups. It would have been obvious to one of ordinary skill in the art at the time of filing to modify the method of Hirschbein to specifically comprise the use of dimethylthiuram disulfide as the sulfur transfer agent. One of ordinary skill in the art would have been motivated to make this modification since substituting one of R1-R4 with a methyl group is a preferred embodiment of the Hirschbein invention (col. 3, lines 13-14), and furthermore substituting R1-R4 with hydrogen is also specifically disclosed as a possible substituent for the preferred thiuram disulfide according to formula I. Moreover, Hirschbein clearly suggests that making such substitutions would have produced a compound having similar properties as the dimethylthiuram disulfide compound used in the method of the instant claims, i.e. as a sulfur transfer agent used in phosphorothioate oligonucleotide synthesis (col. 3, lines 54-63).

Agrawal et al. teach a process for synthesizing oligonucleotides on a small or large scale using H-phosphonate monomers. This process results in a coupling efficiency of more than 97% and consumes about 2-2.5 equivalents excess of monomer to support bound 5'-oligonucleoside or 5'-hydroxyl of a growing chain per coupling reaction. In addition, the method of Agrawal et al. does not require a separate capping step because the use of excess activating reagent serves a self-capping function that prevents elongation of failed sequences. The method of Agrawal et al. is flexible and allows for the introduction of an oxidizing agent to an intermediate H-phosphonate to produce different phosphate backbone modifications (see (col. 11, lines 46-49; col. 2, lines 64-68). The method of Agrawal et al. is much more cost-effective than presently available methods (col. 2, lines 29-43).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the method of Hirschbein to comprise the use of excess activator such that a separate capping step is not used and that oxidation could be achieved by the addition of an oxidizing agent to the coupling reaction comprising the excess activator. One of ordinary skill in the art would have been motivated to make this modification since the teachings of Agrawal et al. provides a method that is much more cost-effective than presently available methods.

Therefore, the invention as a whole is *prima facie* obvious over Hirschbein in view of Agrawal et al.

6. Claims 1-7, 9-12, and 20-21, 23-24, 28-31, 33-41 are rejected under 35 USC 103(a) as being unpatentable by Ravikumar et al. in view of Agrawal et al.

Ravikumar et al., in one specific example, teach a method for synthesizing oligonucleotides wherein said method comprised covalently attaching a 5'-O-

Dimethoxytritylthymidine to CPG (controlled pore glass) through an ester linkage in a glass reactor, and deprotecting the 5'-OH of the attached nucleoside using a solution of dichloromethane and dichloroacetic acid (volume/volume). The product is washed with acetonitrile. Then, a 0.2M solution of 5'-O-(4,4'-dimethoxytrityl)thymidine-3'-O-(2-diphenylmethylsilylethyl N,N-diisopropylphosphoramidite) in acetonitrile and a 0.4M solution of 1H-tetrazole (activator in coupling step, col. 6, lines 64-67) in acetonitrile are added and reacted at room temperature for 5 minutes. The product is washed with acetonitrile, and then a 0.05M solution of Beaucage reagent (sulfur transfer reagent) in acetonitrile is added and reacted at room temperature for 5 minutes. This sulfurization step is repeated one more time for 5 minutes. The support is washed with acetonitrile and then a solution of acetic anhydride/lutidine/THF (1:1:8), and N-methyl imidazole/THF is added to cap the unreacted 5'-hydroxyl group. The product is washed with acetonitrile and then treated with 30% aqueous ammonium hydroxide. This process allowed the synthesis of a 5'-TTTTTTT-3' phosphorothioate heptamer (col. 12, lines 35-60).

It is noted that in regards to the 5'-O-deprotected compound, 5'-O-(4,4'-dimethoxytrityl)thymidine-3'-O-(2-diphenylmethyl-silylethyl-N,N-diisopropylphosphoramidite), the diisopropyl group correspond to L1 and L2 in the formula recited in step (c) of instant claim 1, and the 3'-O-2-diphenylmethyl-silyethyl group corresponds to R5, X1 or Pg, in the structures recited in claim 1 of the instant application.

The method for synthesizing oligonucleotides as disclosed by Ravikumar et al. may also comprise wherein the oxidizing agent transfers an oxygen atom, for example wherein the oxidizing agent comprises: iodine/ tetrahydrofuran/water/pyridine or hydrogen peroxide/ water or tert-butyl hydroperoxide or any peracid like m-chloroperbenzoic acid (col. 7, lines 43-52).

However, Ravikumar et al. does not teach treating an extended compound with a mixture comprising an oxidizing and capping reagents in a single step.

Agrawal et al. teach a process for synthesizing oligonucleotides on a small or large scale using H-phosphonate monomers. This process results in a coupling efficiency of more than 97% and consumes about 2-2.5 equivalents excess of monomer to support bound 5'-oligonucleoside or 5'-hydroxyl of a growing chain per coupling reaction. In addition, the method of Agrawal et al. does not require a separate capping step because the use of excess activating reagent serves a self-capping function that prevents elongation of failed sequences. The method of Agrawal et al. is flexible and allows for the introduction of an oxidizing agent to an intermediate H-phosphonate to produce different phosphate backbone modifications (see (col. 11, lines 46-49; col. 2, lines 64-68). The method of Agrawal et al. is much more cost-effective than presently available methods (col. 2, lines 29-43).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the method of Ravikumar et al. to comprise the use of excess activator such that a separate capping step is not used and that oxidation could be achieved by the addition of an oxidizing agent to the coupling reaction comprising the excess activator. One of ordinary skill in the art would have been motivated to make this modification since the teachings of Agrawal et al. provides a method that is much more cost-effective than presently available methods.

Therefore, the invention as a whole is *prima facie* obvious over Ravikumar et al. in view of Agrawal et al.

7. Claims 1-6, 9-11, 15, and 22-34 are rejected under 35 USC 103(a) as being unpatenable by Caruthers et al. (US 4,458,066), in view of Santamaria et al. and Agrawal et al.

Caruthers et al. (US 4,458,066) disclose a method for synthesizing polynucleotides wherein said method comprises deprotection of a 5'-tritylated nucleoside attached to a solid support via a phosphite linkage between 3'-OH of the nucleoside and the solid support (i.e. silica gel; col. 6, lines 1-7). The deprotected 5'-O of the nucleoside attached to the solid support (compound I, col. 6) is then reacted with a 5'-O-protected nucleoside compound comprising a secondary amino group covalently linked to the Phosphorous atom linked to the 3'-O of the nucleoside. The secondary amino group may comprise heterocyclics including tetrazole and unsaturated heterocyclics comprising a ring nitrogen ((col. 7, lines 17-25); see compound R4 of step (c) of instant claim 1). The next step comprises a capping step wherein the unreactive moieties are capped or blocked in order to prevent the formation of several deoxyoligonucleotides with heterogeneous sequences (col. 7, lines 61-68; anticipates claim 31). Oxidation is carried out by reaction with iodine or alternatively with peroxides like tertiary butyl peroxide and benzoyl peroxide (col. 8, lines 38-44). According to Caruthers et al., oxidation should be carried out before further condensation of nucleoside is attempted. Blocking groups are then removed by a mild base, such as ammonium hydroxide (col. 8, lines 50-52). However, the blocking groups can be removed in a step-wise fashion using triethylammonium thiophenoxide in solvent, e.g. dioxane or tetrahydrofuran. Thereafter, the product is treated with ammonium hydroxide to separate the synthesized oligonucleotide from the polymer support by hydrolyzing the ester linkage joining the oligonucleotide to the support (col. 8, lines 54-60; anticipates claims 33-34).

However, Caruthers et al. do not teach wherein capping of the synthesized oligomer comprises treating the oligomer with a capping reagent comprising about one part by volume of acetic anhydride in acetonitrile or tetrahydrofuran, added to about one part by volume of N-methylimidazole and pyridine in acetonitrile or tetrahydrofuran. Additionally, Caruthers et al. do not teach treating an extended compound with a mixture comprising an oxidizing and capping reagents in a single step.

Santamaria et al. describe an automated method for synthesizing oligodeoxyribonucleotides, wherein the synthesized oligomer is capped using a mixture of capping with acetic anhydride and 1-methylimidazole in tetrahydrofuran and pyridine.

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the method for synthesizing oligonucleotides of Caruthers et al. to utilize a capping reagent comprising about one part by volume of acetic anhydride in acetonitrile or tetrahydrofuran, added to about one part by volume of N-methylimidazole and pyridine in acetonitrile or tetrahydrofuran. One of ordinary skill in the art would have been motivated to make this modification since Santamaria et al. clearly discloses that a mixture comprising acetic anhydride, 1-methylimidazole, tetrahydrofuran and pyridine has specific utility as a capping reagent, and absent evidence to the contrary, it would have been obvious for one of ordinary skill in the art to substitute one functionally equivalent capping reagent for another. Additionally, although the Santamaria et al. does not expressly define the volumes of each component in the capping reagent as set forth in the instant claims, absent evidence of unexpected results, it would have been obvious for one of ordinary skill in the art at the time of filing to modify the parameters in a given reaction in order to optimize the results. See, MPEP § 2144.05 that states:

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Agrawal et al. teach a process for synthesizing oligonucleotides on a small or large scale using H-phosphonate monomers. This process results in a coupling efficiency of more than 97% and consumes about 2-2.5 equivalents excess of monomer to support bound 5'-oligonucleoside or 5'-hydroxyl of a growing chain per coupling reaction. In addition, the method of Agrawal et al. does not require a separate capping step because the use of excess activating reagent serves a self-capping function that prevents elongation of failed sequences. The method of Agrawal et al. is flexible and allows for the introduction of an oxidizing agent to an intermediate H-phosphonate to produce different phosphate backbone modifications (see (col. 11, lines 46-49; col. 2, lines 64-68). The method of Agrawal et al. is much more cost-effective than presently available methods (col. 2, lines 29-43).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the methods disclosed in the Caruthers et al. reference to comprise the use of excess activator such that a separate capping step is not used and that oxidation could be achieved by the addition of an oxidizing agent to the coupling reaction comprising the excess activator. One of ordinary skill in the art would have been motivated to make this modification since the teachings of Agrawal et al. provides a method that is much more cost-effective than presently available methods.

Therefore, the invention as a whole is *prima facie* obvious over Caruthers et al. in view of Santamaria et al. and Agrawal et al.

8. Claims 37-38 are rejected under 35 USC 103(a) as being obvious over Caruthers (US 4,458,066) in view of Agrawal et al. and further in view of Krotz et al.

The discussion of Caruthers et al. (US 4,458,066) in view of Agrawal et al. as set forth above is incorporated here.

However, Caruthers et al. does teach the use of the dimethoxytrityl (DMTr) group as a protecting group (see col. 5, line 55). Additionally, Caruthers et al. teach that 5'-O-trityl oligonucleotides can be deprotected by using Lewis acids (col. 22, lines 30-35). However, Caruthers et al. do no teach wherein in the method of claim 1 said deprotecting reagent is a fluoride moiety, or wherein said fluoride moiety is boron trifluoride etherate.

Krotz et al. teach that in regards to the removal of protecting groups such as dimethoxytrityl (DMTr) moieties, mild acids are used to allow detritylation to occur while minimizing depurination. Furthermore, Krotz et al. teach that mild Lewis acids such as zinc bromide or boron trifluoride etherate could also be used for deprotection (col. 5, lines 18-25).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the teachings of Caruthers et al. to include wherein the deprotecting reagent used to remove the DMTr groups from the synthesized oligonucleotide is boron trifluoride etherate. One of ordinary skill in the art at the time of filing would have been motivated to make this modification since Caruthers et al. clearly teach that Lewis acids are useful as deprotecting reagents, and boron trifluoride etherate is disclosed in the prior art as a being functionally equivalent Lewis acid that is specifically useful for removing DMTr protecting groups from oligonucleotides. It would have been obvious to one of ordinary skill in the art at the time of filing to substitute one equivalent Lewis acid for another.

Therefore, the invention as a whole is *prima facie* obvious over Caruthers et al. in view of Agrawal et al. and further in view of Krotz et al.

Conclusion

9. Claims 16-19 are free of the prior art or any combination thereof. Claims 16-19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
April 6, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635